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Disease-a-Month

Chemoprophylaxis of Infectious Diseases

MAXWELL FINLAND

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Disease-a-Month

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Chemoprophylaxis of Infectious Diseases

I. General Considerations and Application to Streptococcal Infections, Rheumatic Fever, Glomerulonephritis and Bacterial Endocarditis

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Part II of Dr. Finland's discussion of the chemoprophylaxis of infectious diseases will appear later in the series.

GENERAL CONSIDERATIONS

THERE can be little doubt that the introduction and widespread use of effective antimicrobial drugs have markedly if not completely altered the clinical course and prognosis of many serious infectious diseases. Even more significant, perhaps, has been the change in the attitudes of the medical profession and their approach to the problems of infection in their patients. The enthusiasm stimulated by the initial and continuing successes achieved by chemotherapeutic and antibiotic agents in some prevalent and dreaded diseases and by the current great popular interest generated by the lay press in all medical subjects, particularly those dealing with therapy, has also led the public and the profession to expect from these drugs more than is clearly justified by their actual achievements. This has been aided and abetted in no small measure by the manufacturers and financial interests who have created a new, rapidly growing and highly lucrative industry employing aggressive methods of advertising and sales which are directed at the medical profession but, in some instances, rival those used in the promotion of patent medicines to the public, and which all too often involve considerable indirect pressure through the subtle use of the lay press to dis-

seminate premature, grossly exaggerated and often unjustified claims.

The proportions to which the burgeoning antibiotics industry has grown were recently described in the opening paragraphs of a paper prepared for an antibiotics symposium in Prague, in May 1959, by Dr. Henry Welch (1), Director of the Division of Antibiotics of the Food and Drug Administration, United States Department of Health, Education and Welfare. He stated:

"In 1942 when penicillin was first introduced into the United States, it is questionable whether anyone realized that this event was the beginning of a new billion-dollar industry. During the first year of commercial production, about 29 pounds of penicillin were made available. In 1958, more than 800,000 pounds were produced. Total antibiotic production was more than 2.5 million pounds in 1958. Although 28 antibiotics are available for use in this country, 80 to 90 per cent of the total production is accounted for by penicillin, streptomycin, and dihydrostreptomycin and the four broad-spectrum antibiotics, chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol.

"It need not be emphasized here that these drugs have had very wide and, in some cases, indiscriminate use. Their remarkable curative powers, more pronounced perhaps in the early days than now, resulted in their being injected, insufflated, given by mouth, spread on every part of the body, sprayed intra-abdominally, intrapleurally, and intravaginally; no surface or cavity of the body has remained inviolate. There are more than 450 antibiotic preparations available for clinical use today, and they run the gamut of injectables, ointments, powders, sprays, capsules, syrups, ear and eye drops, suppositories, troches, tablets, and vaginal bougies. . . .

". . . . Antibiotics are used in animal nutrition for promotion of growth in swine, chicks, and poults. Therapeutic and prophylactic use of large quantities of antibiotics is made for animals such as cows, beef cattle, swine, chicks, and mink. These drugs are now being used as crop sprays to prevent blight in apples, pears, walnuts, and beans and bacterial diseases in tobacco, tomatoes, peppers, and cherries. Studies have been made to show the value of antibiotics in the preservation of vegetables, fish, beef, ham, chickens, and other perishables."

It may be added parenthetically that the 29 lb. of penicillin produced in 1942 were valued at approximately $3,000,000 and probably now could be produced, and in much better quality, for less than $3,000. This rapid and tremendous reduction in cost, as much as any other factor, was responsible for the early and rapid expansion of the use of this antibiotic from relatively small amounts in highly selected patients with serious infections, in which it is highly and almost uniformly effective, to large doses in a great variety of conditions, in most of which there is little if

any justification for its use. That part of the total antibiotic production diverted to the nonhuman uses mentioned by Welch, although these are many and varied, amounts to less than one-twelfth the total production, but some of these uses have caused considerable anxiety (1, 2), which may be quite out of proportion to the concern which should be directed to their improper medical uses.

The extent to which antibiotics are used in hospitals and the magnitude of the impact of that use on the cost of hospital and medical care were noted in 1956 by Altemeier and Cole (3). They pointed out that over one half of all prescriptions now being written are for antibiotics. At the Cincinnati General Hospital, a university teaching institution, the expenditure for antibiotics has steadily increased from nearly $25,000 in 1950 to over $65,000 in 1955, and at the Children's Hospital of Cincinnati the average cost for an over-all patient-day for antibiotic therapy alone was $6 in 1956, and this represented a 50% increase in only 2 years.

It is difficult to estimate what proportion of the total consumption of antibiotics is devoted to prophylaxis in contrast to clearly therapeutic purposes, and, admittedly, it is sometimes difficult to draw the line between such uses. A few years ago the author and his assistants, after having had complete control of the distribution of all antibiotics and general supervision of their use at a large general hospital since their first introduction, relinquished some of that control and placed the responsibility for the prescription of the 2 most widely used, penicillin and streptomycin, entirely in the hands of the hospital staff. Within 3 months, the use of these 2 antibiotics alone increased more than 5-fold even though the sulfonamides were just as readily available and were still being used to about the same extent as before and the broad-spectrum antibiotics were amply provided for any patient or purpose for which their use could be justified.

A similar increase in the use of the broad-spectrum antibiotics (the tetracyclines and chloramphenicol) and erythromycin took place when these too were relinquished from control and routinely provided through the hospital pharmacy. This happened despite the fact that the total number of patients admitted to the hospital had decreased steadily and the over-all use of penicillin and streptomycin had continued to increase. It may be conservatively estimated that less than one fourth of the amount

of antibiotics being used could be justified as being prescribed for the treatment of actual infections in which they are clearly indicated, as judged by documented experience. It may be added that nearly all the beds in this municipal hospital are used for teaching and are under the direction of the staffs of one or another of the 3 medical schools in the city.

There can be little doubt that most of the unwarranted prophylactic uses of antibiotics are based on wishful thinking, a priori reasoning and the failure to accept or even to require the demonstration under reasonably controlled conditions of the effects which this usage is claimed to produce. Thus we have the following authoritative statement (4):

"Neither the antibiotics nor sulfonamides are effective in the common cold. This is in keeping with the lack of effect with these drugs in common virus diseases. Indeed it is common experience in hospital wards for children who are receiving penicillin, Aureomycin, Chloromycetin, Terramycin, sulfadiazine, each alone or in combination, to develop all signs and symptoms of the common cold or grippe, and even influenza. Nevertheless, since secondary bacterial invaders rapidly complicate the common cold producing otitis media, cervical adenitis, sinusitis, or pneumonia, one may introduce these drugs with beneficial results in the more severely affected. Antibiotic therapy is especially indicated for children who have frequent upper respiratory infections and who harbor pathogenic bacteria in the nasopharynx."

In relation to measles in which respiratory complications may be very serious in young infants, the same writer continues in the same vein:

"All young children with measles should be given antibiotic or sulfonamide treatment as soon as the diagnosis is made and continued until two days after the temperature becomes normal."

An evaluation of these recommendations in the light of reports of their application will be considered in another issue, but it is clear that such statements can lead to almost universal use of antibiotics for almost any purpose and that "justification" or rationalization can be found for almost continuous administration in nearly every individual, and literally "from the womb to the tomb." Thus, the pregnant woman would be offered protection by antimicrobial drugs during labor, because it is known that some women may become seriously ill and may even die from puerperal infections; such usage would be recommended for prolonged labor and especially after rupture of the membranes,

instrumentations, abnormal deliveries, etc., because infections occur more frequently under such circumstances. Treatment of the mother under these conditions could also be justified as a means of preventing sepsis in the newborn. At birth the infant would immediately have contact with prophylactic antibiotics when penicillin or some other agent is instilled into the eyes or given systemically to prevent ophthalmia neonatorum. Further, because most babies are now born in hospitals and there have been outbreaks of serious infections in nurseries, all babies would be treated throughout their stay in the nursery, and premature infants would be particularly selected for more intensive coverage because they are known to tolerate infections poorly.* After that a child would be treated for every respiratory or gastrointestinal symptom that appeared, in order to protect against possible complicating infections or against acquiring such infections from others. Of course, admission to a hospital would require prophylaxis against "hospital infections" by spread from other patients, from carriers among the personnel, from the patient's indigenous flora or that of others or from the air or instruments were he to have an operation or any instrumentation. Exposure to infection in the home or elsewhere would call for prophylactic treatment lest the child acquire such infection by contagion. And so on, until later in life, when in congestive failure or after a stroke, protection would be offered to insure against death from respiratory or urinary infection. In between, there would be frequent colds, bruises or other exposures for which additional prophylaxis of varying duration could readily be justified or given in response to demand from the patient or the family or just to "salve the conscience" of the physician or surgeon (5).

Although such a program would hardly be endorsed in its entirety by the majority of physicians today, it certainly approaches the manner in which many of them actually use antibiotics in their practice. Unfortunately, experience has shown that favorable prophylactic results are regularly obtained only in a very limited number of conditions. The anticipated protective effect of the antibiotics more often than not has failed to mate-

* The grave dangers of inept use of drugs as prophylactic agents in these circumstances have been revealed recently and will be discussed in Part II of this monograph.

rialize or, when success is achieved in one infection, others arise in the "protected" person and these are caused by micro-organisms not susceptible to the antibiotics previously used. Moreover, certain antimicrobials which were at first found to be effective in preventing certain susceptible infections later proved ineffective in these conditions because of changes in resistance of the strains or in the bacterial flora present in the hospital or community. The situation may be reversed temporarily with the advent of some new agents, but these in turn lose their effectiveness after extensive use (6).

There are also some types of prophylaxis in which controlled or comparative studies have been carried out by more than one group of observers with divergent results or with different interpretations of the observed effects by the individual groups. Finally, there are situations in which meaningful data from which the prophylactic value of antimicrobials could be assessed are difficult to assemble or are indeed unavailable; and some of these allow free play to the emotional reaction of the individual physician.

In assaying the value of prophylaxis, the conditions under which the prophylactic agents are used as well as the choice of drugs may be the determining factor in their effectiveness and in the reproducibility of favorable effects. Thus, prophylaxis may be applied in one or more of the following situations.

1. A single application or brief course of antibiotic may be given for the prevention of a highly susceptible infectious agent during or following *a single exposure in one individual;* prophylaxis during or immediately after exposure to gonorrhea is an example of such usage.

2. With the discovery of a case of a contagious infection or a carrier of a potentially communicable pathogen, it may seem desirable to treat the intimate contacts simultaneously with the patient or carrier; a case in point would be a diagnosis of meningococcal infection or dysentery.

3. Prophylaxis may be deemed desirable in a situation of increased local or general susceptibility to various bacterial complications, as in patients with congestive heart failure or respiratory paralysis or in the unconscious patient.

4. Antimicrobial drugs have been used in attempts to reduce the incidence of infection following surgical operations or instrumentation either in an initially uncontaminated area or in a known or potentially contaminated field.

5. Antibacterial prophylaxis has been applied as a continuous measure to prevent recurrences of rheumatic fever or for brief periods in the prevention of subacute bacterial endocarditis in patients with acquired or congenital heart disease. It has also been used continuously in patients with chronic or recurrent nontuberculous bronchopulmonary infections in whom it is hoped to prevent relapses.

6. Antibacterial prophylaxis may be deemed advantageous or desirable in large, compact groups, as in boarding schools, hospitals, institutions and army camps, at the beginning of an outbreak of such contagious diseases as streptococcal or meningococcal infections and dysentery.

7. It may be considered desirable to administer antibacterial agents to prevent potentially serious bacterial complications of epidemic viral infections, as in the case of measles or at the time of an epidemic of influenza, and this could be considered useful in all patients with the viral infection in question or could be limited only to susceptible persons, such as cardiac patients, pregnant women, patients with chronic bronchopulmonary disease and emphysema or asthma. These would be relatively brief courses.

It is obviously not possible here to give a detailed critical analysis of all the evidence that has been presented in each situation mentioned and in many others in which prophylaxis has been used or recommended. Instead, a few of the more important situations or those in which there is some basis for evaluation will be discussed. Since the writer has not personally conducted any of these studies on prophylaxis, he can only attempt to evaluate the available reports objectively in the light of other more intimate experiences with antibiotic therapy. The present discussion will be devoted to a consideration of streptococcal infections, rheumatic fever, glomerulonephritis and bacterial endocarditis. Other prophylactic uses in medicine and surgery will be considered in another issue.

STREPTOCOCCAL INFECTIONS AND RECURRENCES OF RHEUMATIC FEVER

More information and better controlled data are available about the use of antibacterial drugs in the treatment and prevention of hemolytic streptococcal infections and in the prevention of initial attacks or recrudescences of rheumatic fever in susceptible persons than for any other prophylactic use. This is true both for prophylaxis in the individual and for mass use in large groups and communities. The available data were reviewed by Wilson (7) in 1949 with particular reference to the sulfonamides and by Denny (8) in 1954, Mozziconacci and Labesse (9) in 1956 and an Expert Committee on Rheumatic Diseases (10) in 1957, after considerable experience with penicillin had been accumulated. Additional data and reviews have been published by Labesse *et al.* (11), Bywaters and Thomas (12) and McEwen (13). Rantz (14) discussed the management of rheumatic fever and prevention of recrudescences in the April 1954 issue of DISEASE-A-MONTH and Hunter and Paterson (15) included a consideration of the prevention of subacute bacterial endocarditis in the issue of November 1956. The most recent recommendations of the American Heart Association and its Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis were prepared late in 1959 and are summarized in the Appendix to this issue.

The status of sulfonamide prophylaxis was summarized by Denny (8) as follows: (1) Sulfonamide prophylaxis in rheumatic subjects in military populations will reduce the incidence of streptococcal infections and rheumatic fever about 85%. (2) Toxic reactions to the various drugs used make it impossible for about 10% of rheumatic patients to continue prophylaxis for any prolonged period, and several deaths due to sulfadiazine prophylaxis have been reported in military populations. Chemoprophylaxis is therefore not without danger. (3) Sulfonamide-resistant strains of streptococci have not proved a problem in rheumatic populations but have made the use of sulfadiazine impractical for prolonged use in military populations. (4) Prophylaxis with sulfadiazine has not eradicated the streptococcus from the throat in most cases and, to be effective, must be used continuously. (5) There is no general agreement on the duration

of sulfonamide prophylaxis to rheumatic subjects, but Denny quotes the American Heart Association Committee on Prevention of Rheumatic Fever as recommending the following in 1953: All persons who have had rheumatic fever or chorea should receive prophylaxis; prophylaxis should be continued throughout the year, and prophylaxis should be continued in children at least to age 18 and in all those above that age for at least 5 years after the attack. (6) Sulfadiazine is at present the sulfonamide of choice. The recommended daily dosage is 0.5 Gm. for children under 60 lb. and 1 Gm. for all other patients.

Since this review was written, some new and long-acting sulfonamides have become available (16), but only one of them, sulfamethoxypyridazine (Kynex), has been used in a large number of cases for the prevention of streptococcal infections (17) and in a few patients with rheumatic fever (18, 19). The studies on rheumatic fever could not be conclusively evaluated because streptococcal infections were infrequent during their use and no control observations were made. However, in a group of 325 Navy recruits given 2 or 3 Gm. of sulfamethoxypyridazine once a week, there was significant protection against the acquisition of streptococcal infections (6.5% compared with 15.8% in controls). Side effects were reported by 7.1% of the treated men, but only 1.7% (2 men) had reactions that were considered serious, namely, fever with a rash. Schultz and Frank (17) on the basis of their observations consider that sulfamethoxypyridazine could be recommended for use in penicillin-sensitive individuals who require prophylaxis.

It is now the general consensus that penicillin, because it is the most active agent available against group A hemolytic streptococci in vitro and the most effective available agent in the treatment of streptococcal infections, is the drug of choice for the treatment and prevention of hemolytic streptococcal infections except in persons who cannot tolerate it because of severe sensitivity reactions. The efficacy of various dosage regimens available before 1954 in eradicating group A streptococci from patients and carriers and its effectiveness as a prophylactic agent led Denny (8) to the following conclusions concerning penicillin prophylaxis. (1) In rheumatic subjects in military populations, penicillin prophylaxis will markedly reduce the incidence of streptococcal infections. Available data indicate that it is probably

more effective than sulfonamides in this respect. (2) Adequate doses of oral penicillin administered over a period of 10 days will eradicate the group A streptococcus from the throat in the majority of chronic carriers (Fig. 1). (3) There are few toxic reactions to penicillin. (4) No penicillin-resistant group A streptococci have yet been reported, but there has not been enough

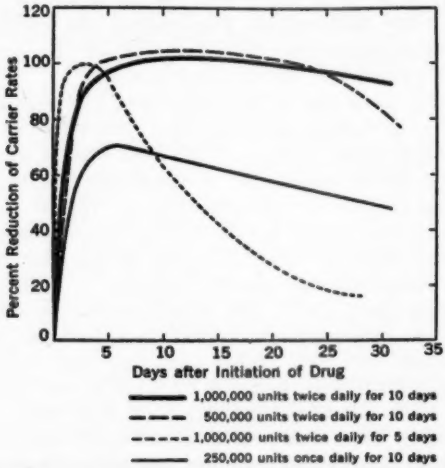

FIG. 1.—Effect of oral penicillin on the carrier state of group A streptococci. (Courtesy of Denny, F. W., Jr.: The Prophylaxis of Streptococcal Infections, in McCarty, M.: *Streptococcal Infections* [New York: Columbia University Press, 1954].)

experience with prophylaxis in large groups over long periods to reach final conclusions concerning the resistant strains.* (5) The chief objections to oral penicillin are that it is relatively expensive and that it should be given on an empty stomach to insure maximum absorption. (6) As in sulfonamide prophylaxis, penicillin should be administered all year round to all rheumatic patients for many years after the initial attack of rheumatic fever. (7) The recommended dosage of oral penicillin for rheumatic subjects is 200,000–250,000 units twice daily.

* No authentic evidence of any significant increases of resistance is known to the author at the time of writing.

PENICILLIN DOSAGE FORMS.—Two distinct advances have been made in penicillin dosage forms which may be helpful in prophylaxis and therapy. One is phenoxymethylpenicillin (penicillin V), which provides higher and better sustained levels than equivalent amounts of penicillin G. Unlike penicillin G, which requires co-administration of buffers and is best administered on an empty stomach, absorption of penicillin V is more complete, is unaffected by the acid of the stomach and hence can be taken

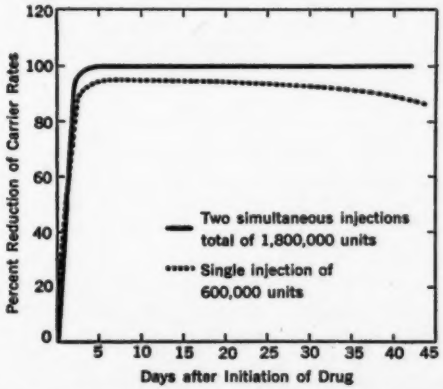

FIG. 2.—Effect of benzathine penicillin G given intramuscularly on the carrier state of group A streptococci. (Courtesy of Denny, F. W., Jr.: The Prophylaxis of Streptococcal Infections, in McCarty, M.: *Streptococcal Infections* [New York: Columbia University Press, 1954].)

at any time without significant loss of activity (20, 21). This, however, is not true of the first semisynthetic penicillin to be introduced, namely, α-phenoxyethyl penicillin (Syncillin, Maxipen); the absorption of this form, according to Cronk *et al.* (22), is markedly reduced when given with or soon after a meal. For parenteral administration, there has come into general use a long-acting repository preparation, benzathine penicillin (N,N'-dibenzylethylenediamine dipenicillin G; Bicillin), which permits a demonstrable penicillemia for a period of a month from a single injection of an appropriate amount (23). Eradication of streptococci with this dosage form is more regularly attained and is more lasting (Fig. 2).

A few relevant studies shed further light on the current problem of prophylaxis. Mohler, Wallin and Dreyfus (24) called attention to the failure of patients to follow a prescribed oral regimen of continuous prophylaxis. In their studies on 245 patients treated with penicillin in their homes even for as brief a period as 7 days, about one-third admitted not taking the prescribed course. Similar difficulties were reported by Feinstein *et al.* (25). This failure to carry through the prescribed medication was just as common among patients receiving medication without charge through public assistance as in others and was considered a serious problem in the effective treatment of ambulatory patients with streptococcal infections and in the prophylaxis of rheumatic fever (24).

Mohler *et al.* (26) also found that for keeping the throat free from beta hemolytic streptococci a single intramuscular injection of benzathine penicillin was more effective (94.4% of patients for 21 days) than a 7 day course of penicillin given by mouth (82.4% for 10 days). Benzathine penicillin also had the advantages of being less expensive than other standard forms of treatment for streptococcal pharyngitis and of eliminating the problem of patient reliability in taking oral medication. However, approximately 70% of the patients complained of discomfort at the site of injection for an average of 2½ days. On the other hand, systemic reactions were very few (0.8%).

In another study, Morris and Rammelkamp (27) administered benzathine penicillin G in a single intramuscular injection to a military population during an epidemic of streptococcal pharyngitis in three different doses: 1,200,000 units, 600,000 units and 300,000 units. Each of the three doses was found effective in eradicating streptococci from carriers. The duration of protection provided by each dose as determined by the development of exudative pharyngitis due to group A streptococci was 6–7 weeks, 4–5 weeks and 1–2 weeks, respectively. The dose of 1,200,000 units was thus the most effective, and this was also found to be the case in another military group (28).

Breese and Disney (29) compared the intramuscular use of benzathine penicillin G with that of 5 different oral preparations, including penicillin V, as to their effectiveness against streptococcal infections in children. All the regimens tested showed uniformly good immediate results. The final result over a 2-month period

indicated that benzathine penicillin G was superior to the oral preparations both therapeutically and prophylactically, was cheaper than the oral preparations and was not associated with the problems of oral administration. They also found no significant difference in the allergic reaction rate of the two methods of administration. The only disadvantage was in painful local reactions frequently observed after injection and the psychologic trauma engendered by the use of the needle. For therapy, considering the cost, they found buffered penicillin G in a dosage of 600,000 units daily for 10 days to be their first choice for *oral* treatment of streptococcal infections in children.

In another study, Breese *et al.* (30) were unable to demonstrate any difference in the initial response to therapy or in subsequent recurrences or carrier rates in patients treated orally with penicillin alone or with penicillin plus a sulfonamide. They concluded that the addition of sulfonamides to penicillin offers no therapeutic advantage.

OTHER ANTIBACTERIAL AGENTS.—In patients who are unable to tolerate penicillin, other alternatives are available in addition to the sulfonamide drugs. Chlortetracycline (Aureomycin) therapy was found by Houser *et al.* (31) to eradicate streptococci from the oropharynx in a large number of instances and to inhibit the formation of antistreptolysin in patients with streptococcal infections; this therapy also greatly reduced the subsequent incidence of rheumatic fever. However, compared with penicillin, chlortetracycline was found less effective in eradicating streptococci, in decreasing antistreptolysin formation and in preventing rheumatic fever. Similar results were reported for oxytetracycline (32).

On the other hand, better effects were reported in the treatment of streptococcal infections and in the inhibition of antistreptolysin O formation with erythromycin. Haight (33), in a controlled study of scarlet fever among naval personnel, showed that erythromycin was apparently as effective as procaine penicillin in treatment of the disease and in prevention of suppurative complications. The incidence of toxic effects was significantly less in the erythromycin-treated patients.

In another study Haight *et al.* (34) observed the effects of various dosage regimens of erythromycin on group A streptococcal infections and on the eradication of the organisms. Treat-

ment was increasingly effective in eradicating streptococci the longer it was administered, up to 7 days, the longest period tested; only 13% of those treated for 1 week had positive cultures on the 21st day. The authors concluded that erythromycin was effective in the clinical management of streptococcal infections but that probably longer duration of therapy and possibly larger doses (they used only 800 mg. a day) would be necessary for adequate eradication of streptococci from patients who continue to harbor the organisms following an acute infection. A dosage of at least 1 Gm. daily, given for 10 days, should prove more effective and the regimen no more difficult to carry out.*

COMMUNITY CONTROL PROGRAM.—An interesting report has been published recently on the successful application of a control program on a community basis. Phibbs *et al.* (35) instituted a program for reducing the incidence of streptococcal disease in a system of primary schools in Casper, Wyoming, an area of high prevalence of hemolytic streptococcal infections and rheumatic fever. All children with symptoms of respiratory infection were inspected daily; a culture was made from the nasopharynx of every child with signs of streptococcal infection; any child found infected with beta hemolytic streptococci was excluded from school until antibiotic therapy had been started or (if such therapy was refused) until a negative culture was obtained. The program was found to be workable without any disruption of school routine. Enforced treatment or exclusion from school of infected children was found to be practical and effective in reducing the incidence of rheumatic disease in the three years of observation. The program involved a minimum expenditure of money, materials and help, and simplified procedures were adopted when possible in attempts to detect and treat the maximum number of streptococcal carriers in the easiest way (36). It appeared probable that this program was also effective in lowering the incidence of new cases of acute nephritis. The program was apparently well accepted by the members of the community and was extraordinarily efficacious as an educational effort.

* Optimum absorption of erythromycin with the highest and best sustained antibacterial activity in serum and without depression in the serum levels by food may be obtained with the lauryl sulfate salt of erythromycin propionate (Ilosone Lauryl Sulfate) (34a, 34b).

Effect on carriers of penicillinase-producing staphylococci.—One new factor has been recognized recently as a possible important complication of penicillin usage which may reduce its effectiveness in therapy and possibly also in prophylaxis of streptococcal infections and rheumatic fever. This involves the occurrence and overgrowth of penicillinase-producing staphylococci that have been shown to interfere with the action of penicillin during treatment of scarlet fever and may account for the failures to eradicate the streptococcus, the early recrudescences and the development of suppurative complications despite therapy (37). This complication may also have been responsible for the failure of Gray (38) to eradicate streptococci from a maternity ward during an outbreak of streptococcal infections. In that outbreak, it apparently was more difficult to clear the streptococci from the nasopharynx of members of the hospital staff than from patients, most of the staff members having acquired the streptococci as carriers and, when they had infections, showing little in the way of manifest illness.

This complication may be of considerable importance during periods of hospitalization and in some persons may continue after release from the hospital if their staphylococcus-carrier state persists. The extent to which this may actually have been interfering recently with penicillin prophylaxis in rheumatic patients is not known.

Duration of prophylaxis.—There has also arisen some controversy over the duration of prophylaxis in patients who have had rheumatic fever or have rheumatic heart disease. It is generally conceded that prophylactic therapy should be continuous throughout periods of possible exposure to streptococcal infections. This has been generally interpreted as continuous prophylaxis in children so long as they attend school and in adults for about 5 years. Bywaters and Thomas (12) consider that duration of prophylaxis is a matter for individual judgment, taking into account parental attitudes, types of exposure and other circumstances. On the basis of their figures for recurrence rates, they believe prophylaxis should continue for at least 5 years after the last attack or until the child has left school, whichever is longer. If, after leaving school, patients are exposed to an increased risk of streptococcal infections, as, for example, when they enter a university or military service, prophylaxis

should be continued for a further period. If liability to reinfection is based on M antibody level, it may be that even more prolonged prophylaxis will be necessary.

A more extreme view has recently been expressed by Mortimer and Rammelkamp (39). After reviewing the frequency of recurrences after varying periods of freedom from attacks and finding some patients with definite recurrences after 10 or more years, they concluded that "certainly, one should not discontinue the prophylactic regimen just because recurrence has not been observed for 5–10 years." They also presented data which indicated that in adults reliance could not be placed just on treatment of streptococcal infections to assure protection from recurrences of rheumatic fever; since many streptococcal infections are inapparent, prophylaxis should be continuous. Moreover, they felt that there was still some doubt whether therapy of the respiratory infection actually prevents cardiac damage. As a result of their analysis, therefore, they recommended that prophylaxis should be maintained indefinitely except in those rare persons in whom the risk of contracting a streptococcal infection is negligible.

COMPARATIVE EFFECTIVENESS OF AVAILABLE AGENTS.—Mozziconacci and Labesse (9) summarized the best available data on the prophylaxis of rheumatic fever and the treatment of streptococcal infections late in 1956 as follows:

1. Continuous chemoprophylaxis with sulfonamides is satisfactory and yields 86% reduction in recurrences, compared to untreated controls. However, treatment of streptococcal infections with sulfonamides is probably not effective since it produces only a temporary reduction in convalescent carrier rates of streptococci and no reduction after 2 weeks or longer; there are no actual figures on the effectiveness of sulfonamide therapy of streptococcal infections in prevention of subsequent attacks of rheumatic fever.

2. Oral penicillin is both an excellent method of continuous prophylaxis of rheumatic fever and an effective treatment of streptococcal infections, yielding a 93% reduction in rheumatic fever rates in the former and 75–85% in the latter usage.

3. Penicillin in oil and aluminum monostearate given in 4 doses of 600,000 units each at 48-hour intervals is as effective in therapy of streptococcal infections as oral penicillin and produces an 80% reduction in the carrier rate during convalescence.

4. Benzathine penicillin G, 1,200,000 units monthly, insures continuous prophylaxis (90% reduction in recurrences of rheu-

matic fever) in convalescent rheumatic fever patients and is equal or superior to oral penicillin in treatment of streptococcal infections.

5. Chlortetracycline is about 80% effective for reducing recurrence rates during continuous prophylaxis, but during convalescence this agent or oxytetracycline reduces the carrier rates in only about one-half the patients. These agents, therefore, are definitely inferior to penicillin for these purposes.

6. Allergic reactions are more common after 1,200,000 units of benzathine penicillin than after 600,000 units intramuscularly or after continuous oral penicillin.

7. Continuous chemoprophylaxis with penicillin does not involve any serious dangers from modification of the pharyngeal flora. However, staphylococcal infections have been observed frequently in rheumatic subjects during penicillin prophylaxis and these persist in hospitals but subside readily at home.

These authors concluded that continuous prophylaxis is best provided by penicillin, but if this form is not possible, sulfonamides are the second choice and chlortetracycline the last. Therapy of streptococcal infections is carried out best with penicillin, with one of the tetracyclines as second choice but not with sulfonamides. The chief advantage of benzathine penicillin is that it insures continuity of treatment; its chief drawbacks are the uncertainty of sustaining adequate blood levels and the frequency of allergic reactions. In practice, however, it gives excellent results clinically, and sensitivity reactions are rare in children.

The dosage regimens recommended by these authors are:

A). For prophylaxis: penicillin G, 200,000 units, or penicillin V, 100,000 units, each given twice daily; or benzathine penicillin, 1,200,000 units once a month or 600,000 units twice a month; or sulfadiazine, 0.5–1 Gm. daily. Prophylactic therapy should be continuous for at least 5 years and in any case up to age 15; however, this should be more vigorous in patients who already have cardiac involvement.

B). For the treatment of streptococcal sore throats: oral penicillin G, 200,000 units, or penicillin V, 100,000 units, each given 4 times a day for 10 days; or procaine penicillin, 3 injections of 300,000 or 600,000 units every 48 hours; or benzathine penicillin, 1 injection of 1,200,000 units; or one of the tetracyclines, 2 Gm. daily in divided doses for 10 days. Acute sore throats in rheumatic subjects should always be regarded as streptococcal in origin and

treated vigorously with penicillin despite the fact that a precise diagnosis is possible only in about 75% of patients.

Prevention of Cardiac Lesions in Patients With Active Rheumatic Fever

The question has been raised as to whether treatment of active rheumatic fever, or indeed of hemolytic streptococcal infections, has any effect on the subsequent development of rheumatic carditis. Data presented by Weinstein *et al.* (40) in a 7-year follow-up of a group of 110 patients with scarlet fever treated with penicillin in 1946, suggested that penicillin therapy of streptococcal pharyngitis in children, even when applied early, may not have significantly decreased the occurrence of rheumatic carditis. Their evidence suggests that in children the clinical features of the acute rheumatic state may be markedly suppressed by chemotherapy of the initiating streptococcal infection, so that most or all of the characteristic signs and symptoms are absent. Under such circumstances the abnormal electrocardiographic findings become the most prominent and sometimes the only diagnostic features. Weinstein *et al.* therefore feel that it may be necessary to redefine the criteria for the diagnosis of acute rheumatic fever, particularly in children whose streptococcal pharyngitis is treated with antibiotics. They suggest that the demonstration of a prolonged atrioventricular conduction time after a latent period may be of great significance for diagnosis of rheumatic carditis in the absence of "major" manifestations if the patient has had a recent streptococcal infection.

On the other hand, Mortimer *et al.* (41) in a controlled study of 97 patients with acute rheumatic fever found that 6 weeks of intensive penicillin therapy, although it appeared to have no effect on the acute clinical, laboratory and electrocardiographic manifestations, did, nevertheless, appear to produce a reduction of probable statistical significance in the incidence of valvular heart disease a year later. They suggest that the disparity between the effects on the acute phase manifestations and those on the endocardial lesions may indicate that these processes differ pathogenetically, and they also feel that their data indicate that the living streptococcus continues to play a significant role in the development of valvular heart disease even after symptoms of

rheumatic fever have appeared. They therefore conclude that an intensive course of penicillin may be important in therapy of acute rheumatic fever for its effect on valvular heart disease. The findings of Mortimer *et al.* are certainly provocative but cannot yet be considered conclusive; they require confirmation before they can be accepted. It should be recalled, also, that Swift *et al.* (42) had earlier shown that sulfonamides have no favorable effect on acute rheumatic fever and indeed are considered to be contraindicated. However, it may be argued that the failure of sulfonamides to eradicate streptococci during streptococcal infections may account for this lack of favorable effect in rheumatic fever and that penicillin, which eliminates streptococci effectively, may have the desired effect of avoiding the continued stimulation from the presence of the streptococcal antigen.

ACUTE GLOMERULONEPHRITIS

The problems involved in the application of antibiotics and chemotherapeutic agents to the treatment and prevention of streptococcal infections with relation to the occurrence of glomerulonephritis have recently been discussed by Rantz (43) and Haight (44). It is now clear that, of the more than 40 specific types of group A beta hemolytic streptococci that are now known and identifiable, only a small number are involved in the streptococcal infections that precede acute glomerulonephritis. Type 12 is by far the most common, but cases associated with types 4, 19 and 25 also occur and on rare occasions other types or untypable strains have been identified. Outbreaks of infections due to some of these "nephritogenic" strains do occur and are associated with a high incidence of nephritis. During such periods it is important to eradicate these strains as far as possible both from patients and from carriers among patient contacts. A single dose of benzathine penicillin, 600,000 units, in children weighing less than 60 lb. and 1,200,000 units in others should be sufficient, or a 10-day course of oral penicillin or of erythromycin may be used when injections are not desired or penicillin is not tolerated.

The value of chemoprophylaxis in the patient who already has glomerulonephritis is not defined as well as it is in the patient with rheumatic fever. Specific immunity to the causal nephritogenic streptococcus is acquired after infection and it is highly

unlikely that the individual will come in contact with another nephritogenic strain. Nevertheless, it has been demonstrated that infection by hemolytic streptococci is the commonest cause of exacerbation of chronic nephritis; Rantz (43) therefore considers it desirable to protect the patient against these organisms while healing of the acute lesion is in progress and he recommends 1,200,000 units of benzathine penicillin G intramuscularly at monthly intervals for 6 months. Oral therapy with either penicillin or sulfonamides would not be recommended because it is less reliable; moreover, sulfonamide drugs are not desirable and probably should not be used in patients with nephritis because of the danger of drug retention and the possibility of further renal damage. Broad-spectrum antibiotics likewise cannot be recommended because they are less reliable than penicillin for eradication of streptococci.

Prophylaxis in Contacts of Patients

How far one should go with prophylaxis and treatment of contacts of patients with rheumatic fever or nephritis may also be a matter of controversy. In glomerulonephritis it would seem important both for the good of the persons involved as well as for the community to attempt to eradicate all streptococci from carriers. Presumably this would include all members of the patient's family, because family contacts are frequently found to harbor the same streptococci and may even show evidence of latent glomerulonephritis. Treatment of household contact carriers of hemolytic streptococci in the families of rheumatic patients may also be desirable, although less urgent since the patient himself is receiving continuous prophylaxis. On the other hand, should a hemolytic streptococcal infection develop in a rheumatic patient, a course of therapy for eradicating streptococci from the household contacts may be very desirable. A single dose of benzathine penicillin would be the treatment of choice, although any of the alternatives previously mentioned may be used.

SUBACUTE BACTERIAL ENDOCARDITIS

The prevention of rheumatic fever is relatively simple because the major and essentially the only recognized etiologic relationship is with group A hemolytic streptococcal infections and these are

all highly susceptible to penicillin. As a result, the prevention of hemolytic streptococcal infections and of rheumatic fever is on a firm basis. Moreover, because relatively small doses are used and rather low concentrations of antibiotic are maintained in the body, there appears to be little danger of the predominant bacterial flora of the pharynx or intestine being replaced by antibiotic-resistant pathogens during the prophylactic regimens used. Some increases in prevalence of certain organisms of lesser susceptibility to penicillin have been noted in the nasopharynx, but such organisms rarely become the predominant flora, as shown in studies of Miller and Massell (45).

The same cannot be said for antibiotic prophylaxis of subacute bacterial endocarditis. The kinds of streptococci that cause this condition are universally present in the respiratory tract even of normal individuals, they vary in susceptibility to drugs, being generally much less sensitive that the group A hemolytic streptococci, and they are practically impossible to eradicate permanently. Moreover, recent evidence suggests that there has been an increase in cases of subacute bacterial endocarditis caused by enterococci which are considerably less susceptible to penicillin and many other antibiotics.

The subject of prophylaxis of subacute bacterial endocarditis was reviewed by the author (46) in detail in 1954 and his specific recommendations for such prophylaxis have been published more recently (47). The major observations in these papers are summarized here, with omission of most of the references which can be found in the original review.*

Almost all writers concerned with antibiotic therapy of subacute bacterial endocarditis recommend that susceptible persons, chiefly those with valvular or congenital heart disease, be given an antibacterial agent, particularly penicillin, during dental extractions. Routine use is also advocated in relation to certain other types of operations or procedures, including the antepartum and postpartum periods and the pre- and postoperative periods of prostatectomy and other genitourinary operations, and also during various diagnostic procedures and instrumentations. Sulfonamides have been used in the past and broad-spectrum anti-

* The practical features were also noted by Hunter and Paterson in the November 1956 issue of DISEASE-A-MONTH.

biotics have been suggested in relation to operations and other procedures; supplementation with streptomycin appears to be preferable to use of penicillin alone in such situations, because organisms of moderate or high resistance to penicillin are somewhat more common in the cases of endocarditis that follow such manipulations than in those following dental extractions. Moreover, Lichtman and Master (48) found valvular lesions at autopsy in most persons over age 60, and these lesions often go unrecognized during life. They, therefore, recommended prophylactic antibiotics for all persons over age 50 who undergo diagnostic or manipulative procedures.

These recommendations may have a sound basis in principle and from a practical clinical point of view, but it is important to point out that (1) the value of the procedure has never been proved, and (2) the possible risks and dangers involved have never been evaluated. There is as yet no valid proof that prophylactic procedures according to any of the programs recommended thus far have actually prevented any significant number of cases of bacterial endocarditis. It is of course well known that in a large proportion of cases of bacterial endocarditis symptoms appear in a significant temporal relation to dental or other surgical manipulations. However, the only substantial evidence that has been advanced in support of the recommendations for chemoprophylaxis has been the reduction in the immediate bacteremia in persons pre-treated with sulfonamides, penicillin or chlortetracycline. It may be added, also, that the strains of nonhemolytic streptococci cultured from the mouth in the areas of dental sepsis closely resemble those obtained from the blood of patients with bacterial endocarditis. Krumwiede (49) had also shown that while the nonhemolytic streptococci from rheumatic children receiving penicillin prophylaxis are more resistant than those from control children not on penicillin, they are not as resistant as some strains from patients successfully treated for subacute bacterial endocarditis, and strains of similar resistance occur in untreated patients.

Although these are important and well documented observations, they cannot be accepted as adequate proof of the value of the same procedures in preventing the occurrence of bacterial endocarditis. Indeed, such proof would require long term follow-up of large numbers of susceptible persons in whom similar dental

procedures are carried out in comparable cases, with or without prophylaxis, to obtain statistically valid comparisons. The number of cases that would have to be studied is suggested by the calculation indicating that the risk of an attack of subacute bacterial endocarditis after any tooth extraction in a susceptible patient is approximately 1 in 533. No data approaching this magnitude have yet been presented.

There has also been some suggestion that extraction of all teeth should be recommended to prevent recurrence of subacute bacterial endocarditis on the basis of preliminary observations; the data offered cannot be considered as proof of the effectiveness of such a radical procedure. On the other hand, several cases have been reported in which subacute bacterial endocarditis, or relapse in a cured case, followed tooth extraction even though the extraction was carried out under chemoprophylaxis, the interval being short enough to suggest that it probably resulted from that episode.

Of interest in this connection is the report of Dormer (50) on the patients with bacterial endocarditis who were treated at St. Bartholomew's Hospital between 1945 and 1956. In 11, the history strongly suggested that extraction of infected teeth without antibiotic cover was the precipitating factor. In 2, however, infection followed dental extractions despite penicillin prophylaxis. In addition, 1 edentulous person was infected with green-producing streptococci which proved to be highly resistant; this patient had an infected ulcer of the mouth caused by an abrasive effect of ill-fitting dentures and his infection may have resulted from this. Dormer recommends that dentists should ask simple questions regarding heart disease and rheumatic fever before extracting teeth. All patients known to be a risk should have regular and close dental care, and adequate examination of patients not often seen should include x-rays of the teeth. All extractions in susceptible patients should be performed "under antibiotic cover." After such extractions, and because antibiotic cover does not always prevent infection, patients should be specifically warned to report early should untoward symptoms arise.

The seriousness of the disease that one is attempting to prevent would warrant a certain amount of risk if the procedures recommended could be proved efficacious. These risks, apart from untoward reactions and the possibilities of sensitization, have not

been clearly defined and may be difficult to quantitate. However, there is some evidence that significant changes take place in the flora of the mouth during prophylactic use of penicillin, especially when moderate or large doses are used, and also during administration of broad-spectrum antibiotics and erythromycin. These changes involve a moderate but probably significant increase in resistance of the common alpha hemolytic or nonhemolytic streptococci as well as a rise in the number and proportion of gram-negative organisms and in the numbers and resistance of staphylococci. Antibiotic prophylaxis, therefore, may result in a reduction in the relative number of organisms susceptible to the prophylactic agent but may also involve the definite possibility of an increase in proportion, and perhaps in the total numbers, of those that are relatively or highly resistant to that agent (6) and these may, in turn, invade the blood stream, implant themselves on the damaged valve and result in infection which may be difficult to treat.

These remarks should not be interpreted as indicating that a case against the use of antibiotic prophylaxis has been made. The frequency with which dental extractions, surgical procedures and diagnostic instrumentation are noted as antecedent events is sufficient to warrant continuing such usage unless or until it can be shown to be ineffective or harmful. These remarks are meant, however, to point out that there are no data from which one can determine with any degree of assurance the following points: whether or not treatment before actual time of dental manipulation or other procedures is of any importance and, if it is, for how long before the procedures such prophylaxis should be applied; the optimum agent or agents for any given type of operation or procedure; the proper dosage for prophylaxis; the optimum duration of administration. It is also meant to point out the need for realizing that such a procedure is not without a certain risk and that data are not yet available but are urgently needed from which these risks could be measured and compared with any potential benefit from the prophylactic use of antibiotics.

The highly successful results of the surgical closure of patent ductus arteriosus offer a prophylactic measure of first magnitude for both initial attacks and for recurrences of bacterial endocarditis in patients with this congenital anomaly. This procedure may also be a major factor in the cure of active cases of endocarditis in such patients. The same antibiotic treatment that is

indicated for the infecting organism is usually recommended and carried out before surgery is undertaken in patent ductus arteriosus complicated by bacterial endocarditis, and the operation may be successfully performed during the course of therapy for subacute bacterial endocarditis. However, recovery based on the surgical procedure alone without the use of chemotherapy or antibiotics has been recorded. Indeed, patients have been cured by the operation after failure of antibiotic treatment alone. Surgery is therefore indicated for patent ductus arteriosus even after patients have been cured of bacterial endocarditis. Recurrent infection of these patients is rare but occur after operation.

As already mentioned, bacteremia with streptococci of the viridans group is the predominant type demonstrated during dental manipulations, but invasion of the blood stream with enterococci or with various coliform organisms may occur soon after instrumentation or operation on the infected genitourinary or intestinal tract. These facts, coupled with the history of such procedures antedating onset of the infection in a large proportion of patients with bacterial endocarditis, strongly suggest that measures directed at preventing the bacteremia or eliminating the organisms from the blood stream as rapidly as possible are highly desirable.

The only available method to accomplish this, other than the obvious one of minimizing trauma to tissues during the procedures, is the use of antibacterial drugs. Since endocarditis due to organisms of the types found in the mouth affects primarily persons with valvular or congenital cardiac lesions, prophylaxis during dental manipulation is indicated principally but not solely in such individuals. Endocarditis caused by enterococci or other enteric organisms, on the other hand, may occur even on apparently normal valves, so that prophylaxis would seem indicated after manipulations of the infected genitourinary or intestinal tract of all patients. However, there are no data from controlled experience on which to base any reasonable recommendations as to the choice of antibacterial agents and dosage or the time and duration of administration in relation to such procedures.

The only reasonable assumptions upon which such recommendations can be based are that manipulations in the oral cavity would be associated with the relatively sensitive streptococci viridans group and that bacteremia resulting from operations or instrumentation on the genitourinary or intestinal tract would be associated with organisms of the common intestinal flora or those

commonly found in infections of the urinary tract, namely, enterococci and coliform organisms. In patients who are already under antibiotic treatment or have had treatment recently, the flora may be expected to consist of organisms moderately or highly resistant to the antibiotics being used. In any event, eradication of organisms from the circulating blood before they have become implanted should be possible with appropriate antibiotics in relatively lower doses and in much briefer periods than after endocarditis is already established. The possibility of sequestration and possibly of protection of the organism from circulating antibiotics, particularly inside phagocytic cells, however, must also be considered.

On the basis of these considerations, the following recommendations for prophylaxis of bacterial endocarditis were made (47):

In patients with known valvular or congenital cardiac lesions undergoing dental manipulations and in whom penicillin is not contraindicated because of hypersensitivity, a single intramuscular dose of 600,000 units of aqueous procaine penicillin G plus 200,000 units of sodium or potassium penicillin G should be given just before the procedure and this dose may be repeated in a few hours. Benzathine penicillin should probably not be used because of the lower circulating levels of antibiotic that result from this form. A somewhat larger dose of penicillin, supplemented by 500 mg. or 1 Gm. of streptomycin, may be used as an additional factor of safety, especially in patients who have had rheumatic fever and are receiving penicillin prophylaxis. Attempts to sterilize the dental field prior to extractions or other procedures by prolonged intensive treatment have little likelihood of success. On the other hand, such therapy may offer an opportunity for invasion by organisms highly resistant to the agents used for the prophylaxis and would thus defeat its purpose. However, mixtures of bacitracin and neomycin in troches may be used after dental extractions even though the actual value of their use is not known. They have possible merit in that there are not likely to be any important pathogenic organisms resistant to these agents in the mouth and these antibiotics would not ordinarily be selected for systemic use should infection occur.

Extraction of all teeth seems indicated only when most of them are carious and when there is extensive periodontal sepsis; this does not seem warranted as a routine procedure on the basis of the small amount of data available.

A prophylactic regimen for use during genitourinary or intestinal procedures is more difficult to formulate. For anticipated invasion by enterococci, a combination of a large dose (1,200,000 units) of penicillin plus 1 Gm. of streptomycin would seem reasonable. This may be of some value against streptomycin-sensitive coliform bacteria but would be inadequate against most other gram-negative bacilli, particularly Pseudomonas, Proteus, or Aerobacter, a great majority of these and perhaps other coliforms now being resistant to streptomycin and to penicillin. Addition of chloramphenicol or tetracycline to this combination may be suggested, but here again increasing proportions of these gram-negative organisms are found which are resistant to these antibiotics. Treatment with antibiotics should best be started within 1 or 2 hours of the procedure and continued over a period of at least 24–48 hours.

Bacterial Endocarditis Following Cardiac Surgery

The introduction of intracardiac surgery for rheumatic and congenital heart disease has provided a new source for the development of bacterial endocarditis, since the procedure entails trauma to both normal and abnormal endocardium. On the basis of examination of 2,263 patients operated upon for acquired and congenital heart disease during a 5-year period ending November 1955, Denton *et al.* (51) concluded that bacterial endocarditis is a rather infrequent complication of surgery but, when it occurs, is caused by organisms not commonly encountered in patients not operated upon and carries a high mortality rate. Twenty cases of bacterial endocarditis occurred in this series, 1 among 374 cases of congenital heart disease and 19 among 1,889 cases of acquired valvular heart disease. About one-third occurred early (within 10 days after surgery), one-third late (more than 3 months after surgery), and the remaining third were in the intermediate group. The most common infecting organism was the staphylococcus (14 cases), the coagulase-negative variety more frequent than the coagulase-positive ones. These organisms were generally quite resistant to penicillin both in vitro and clinically. Despite treatment with a variety of antibiotics, usually given in fairly massive doses, only 8 of the patients survived. Most had received large doses of antibiotics before and for a 10-day period after surgery; this

antibiotic program always included penicillin. The authors considered that antibiotic prophylaxis could be approached rather conservatively but that, once bacteremia has developed, therapy should involve the use of large doses, with the antibiotic being chosen on the basis of sensitivity of the organisms recovered from the blood stream.

Hoffman *et al.* (52) reviewed a series of 40 cases of bacterial endocarditis that followed cardiotomy for acquired heart disease. There was little information available in these cases regarding antibiotic prophylaxis for rheumatic heart disease or the use of antibiotics following cardiotomy. However, it appeared unlikely that any significant number of the patients were receiving continuous penicillin prophylaxis for rheumatic fever. It was also reasonable to assume from some of the information available that all of the patients were probably given some antibiotic during the hospitalization for the valve surgery. Penicillin was the antibiotic of choice and was frequently combined with streptomycin. Information was incomplete on the prophylactic antibiotics prescribed when a patient had been discharged from the hospital after the operation and before the episode of bacterial endocarditis.

These authors derived the impression that bacterial endocarditis developing in the immediate postoperative period (1–4 weeks) is related to extracardiac sources possibly introduced at the time of surgery, as opposed to the difficulty in demonstrating the source of infection in cases developing in the late postoperative period (longer than 4 weeks). In their series, too, staphylococcus was the commonest causative organism, being found in the blood in 26 patients; in 11, the staphylococci were coagulase positive and in 15, coagulase negative. Of the 11 patients with coagulase-positive staphylococci, 6 survived; of the 15 with coagulase-negative organisms, 7 were living at the time of report, suggesting only that coagulase-negative strains predominated and carried a high mortality, as they did in Denton's series.

There has been no definite study in any large series to determine the value and choice of prophylactic antibiotics or the importance of dosage and duration of administration postoperatively. Because the staphylococcus is the most common organism, it might be suggested that vancomycin be given intravenously for a day or 2 as soon as possible after cardiac surgery, because this agent

appears to be active and is bactericidal in vitro against all strains of staphylococci; or, if the risk of a reaction cannot be taken, the combination of novobiocin orally and bacitracin intramuscularly could be used. However, other organisms including Pseudomonas and enterococci have also been found; only the latter are probably susceptible to these antibiotics.

Another important aspect of the pathogenesis and therapy of staphylococcal infections of the heart and great vessels following cardiac surgery has been revealed in a study by Bahnson, Spencer and Bennett (53). These authors reported 5 cases of staphylococcal stitch abscess of the myocardium and great vessels following surgical procedures. These infections were strikingly resistant to massive antibiotic treatment but complete eradication followed removal of the sutures. The authors carried out experimental studies on the reaction to several materials implanted in the right ventricular myocardium of dogs. In the presence of minimal contamination by staphylococci, the use of silk, stainless steel, Dacron, Nylon and catgut sutures all led to the formation of infected granulomas from which organisms could be cultured for as long as 6 weeks. They noted, however, that the infection associated with catgut subsided regularly and healed spontaneously after 3 weeks, presumably because of the gradual absorption of the foreign body. They were hesitant, however, to recommend the use of catgut sutures because of the great emphasis placed on the use of silk by the surgeons at their institution.

Bacterial Endocarditis after Obstetric Procedures

A number of reports on the value of prophylactic uses of sulfonamides and antibiotics in complicated obstetric cases appeared soon after these agents became available; some of the studies were well controlled and generally indicated that postpartum infections could be either prevented or markedly reduced in severity by the early and routine use of these agents. These reports dealt primarily with the prevention of streptococcal and other susceptible infections and antedated the change in the character of hospital infections that has been occurring over the past decade (54) and which has affected obstetric as well as other patients. It is therefore not possible at present to accept these results at face value. Two recent reports, therefore, are of interest.

Redleaf and Fadell (55) obtained blood cultures immediately after the third stage of labor and on the morning of the first postpartum day in 101 patients. Growth was obtained in 15 of the 202 cultures, 4 among those obtained immediately after delivery and 11 in those drawn on the next day; in no instance were both cultures positive in any patient. Fourteen cultures yielded staphylococci, most of them only in thioglycollate broth, and only 1 was coagulase positive. A single culture yielded alpha hemolytic streptococci; this was from a patient who had inactive rheumatic heart disease and had taken a sulfonamide drug daily prior to labor but, through an oversight, was given no "antibiotic coverage" during parturition. Six subsequent blood cultures in this patient were negative, however, and no clinical evidence of bacterial endocarditis appeared in the next 2 months. Only 3 of the other patients with positive blood cultures had transient postpartum fever; 1 had endometritis caused by a beta hemolytic streptococcus, another had Escherichia coli pyelonephritis and in the third the fever was unexplained. The staphylococci were considered to be contaminants because they were coagulase negative; this, however, may not necessarily be the case, as indicated by the frequency with which such strains produce serious and even fatal endocarditis after cardiac surgery.

These authors reviewed some of the data on the frequency with which subacute bacterial endocarditis has been precipitated by abortion or delivery and they laid particular emphasis on the report of 3 cases of endocarditis among 18 patients who had been given no antibiotic immediately before delivery or after labor, whereas no recurrences or new cases of bacterial endocarditis were identified among 102 patients with known heart disease who received prophylactic therapy. They discussed the choice of prophylactic agents and concluded that the combination of large doses of penicillin with added streptomycin would be advantageous; this therapy, they feel, should be initiated at onset of labor and continued through the third postpartum day "as in other procedures associated with a hazard of bacteremia." The question may well be asked whether or not this regimen or the tetracyclines, which had proved advantageous in some earlier studies, would in fact accomplish the desired protection in view of the prevalence in hospitals of infections with organisms that are predominantly resistant to all these antibiotics.

The same question may be raised with respect to the recommendations made by Lein and Stander (56), who reviewed the histories of 8 patients with subacute bacterial endocarditis following obstetric and gynecologic procedures. All but 1 had a history of cardiac disease, mostly rheumatic, and none had received prophylactic antibiotics. The causative organism was a streptococcus of the viridans group in 5, Staphylococcus aureus in 1 and Pseudomonas aeruginosa in 1; no organism was recovered in 1 case. Four patients died. The authors advocated the combination of 1,200,000 units of procaine penicillin and 1 Gm. of streptomycin followed by one-half this dose every 12 hours for 48 hours after delivery. They indicate that they have not yet seen subacute bacterial endocarditis develop in any cardiac patient who had been prophylactically treated in this manner.

Bacterial Endocarditis after Urinary Tract Surgery

What has been said about obstetric and gynecologic patients applies equally to patients in whom surgical procedures or instrumentations are carried out on the urinary tract. Here, however, there is an even greater risk of invasion by antibiotic-resistant organisms, since most of these patients have had previous exposures to various antibiotics which usually resulted in the elimination of antibiotic-susceptible organisms and their replacement by resistant ones (6). Two reports, an early and a more recent one, are of interest in this regard.

In 1949 Traut and Miller (57) reported on 7 patients who had undergone urologic procedures and 1 a gynecologic operation and died within days or months. Each was found to have bacterial endocarditis at autopsy. All had had rheumatic endocarditis in early life and all but 1 had demonstrable heart disease on admission to the hospital. None had received antimicrobial therapy preoperatively. In only 1 was postoperative bacterial endocarditis recognized clinically. Blood cultures obtained during life were positive in 5 patients, with Streptococcus viridans found in 3 and Staphylococcus aureus in 2. The authors concluded that all patients with a history of rheumatic fever or findings of acquired or congenital cardiac lesions should receive penicillin and a sulfonamide before and following any surgical manipulation of infected tissues. Also, signs of infection following operation should

suggest bacterial endocarditis and the patient treated as a presumptive case.

These conclusions appear justified and reasonable and, with modifications for our current knowledge of the bacterial etiology of postoperative infections, may be recommended today. That there can by no means be any certainty that such prophylaxis would in fact alter the incidence of postoperative infections is suggested by the results of a study of prophylactic use of chloramphenicol in patients subjected to transurethral resection of the prostate gland as reported by Appleton and Waisbren (58). In a strictly alternated series of 100 patients, chloramphenicol being given to 50, no significant beneficial effects were demonstrable in the immediate postoperative complications, the postoperative bacteremia, the postoperative urinary cultures, the duration of drainage, of pyrexia or of hospital stay, or in the mortality. The medication was well tolerated and no toxicity noted. However, the study provided no evidence to justify the prophylactic use of the antibiotic in transurethral prostatic resection. The authors felt that until such evidence is forthcoming, it is questionable whether such usage is justified.

Some of the other problems involved in the prophylactic uses of antibiotics in surgery and in various additional medical conditions will be considered in a forthcoming issue.

APPENDIX

Résumé of Current Procedures Recommended by the American Heart Association for the Prevention of Rheumatic Fever and Bacterial Endocarditis

I. Prevention of Recurrences in Rheumatic Subjects

A. *Continuous prophylaxis* for all patients with *well documented* history of rheumatic fever or chorea or with *definite evidence* of rheumatic heart disease. The safest general procedure is to continue prophylaxis through all seasons indefinitely, particularly if rheumatic heart disease is present. Prophylaxis should be initiated as soon as the diagnosis of active or inactive rheumatic fever is made or thereafter when the patient is first seen; therapeutic doses to eradicate the streptococcus should be given first and followed by the prophylactic regimen.

SPECIFIC METHODS AVAILABLE:

1. *Benzathine penicillin G intramuscularly,* 1,200,000 units once a

month. Avoid in patients giving a history of severe penicillin reactions, particularly angioneurotic edema.

2. *Sulfadiazine,* 0.5–1 Gm. once a day, the smaller dose for children under 60 lb. Rashes and sore throats occurring during first 8 weeks should be considered toxic reactions and the drug omitted. A weekly white cell count should be done during the first 2 months and the drug stopped if it falls below 4,000 and the polymorphonuclear neutrophils fall below 35%, especially if a sore throat or rash is present.

3. *Penicillin,* 200,000 or 250,000 units by mouth once or preferably twice daily. Toxic reactions are similar to, but less frequent than, those after intramuscular administration.

B. *Treatment of streptococcal infection in rheumatic subjects.*—Whether or not the patient is receiving prophylaxis at the time, treatment should be prompt and vigorous. The maximum therapeutic dose (see II, B) should be given and even that will not always prevent rheumatic recurrences once streptococcal infection occurs.

C. *Protection of rheumatic fever patients in hospital wards.*—Continuous streptococcal prophylaxis should be used throughout the hospital stay; oral penicillin, 250,000 units twice daily, is preferred. Patients with active rheumatic fever should first receive a therapeutic dose to eradicate streptococci.

II. Treatment of Streptococcal Infections in the General Population

A. *Diagnosis.*—Bacteriologic support (by throat culture) is highly desirable, otherwise depend on signs and symptoms.

B. *Treatment.*—Start as soon as possible, but an 18–24 hour delay to await results of throat culture does not reduce the efficacy of treatment in preventing the development of rheumatic fever. Penicillin is the drug of choice when used orally; full doses must be used for 10 days to eradicate streptococci from the throat and to prevent rheumatic fever. When possible, a culture should be done 48 hours after the last dose to ascertain absence of streptococci.

RECOMMENDED DOSAGE SCHEDULES:

1. *Benzathine penicillin G,* 1 intramuscular injection of 600,000 units for young children and 900,000 units for children over 10; 900,000 or 1,200,000 units for adults.

2. *Procaine penicillin G* with aluminum monostearate in oil, intramuscularly, 300,000 or 600,000 units every third day for 3 doses for children and adults, respectively.

3. *Oral penicillin G,* 200,000–250,000 units 3 times a day for 10 days, to be completed even though fever and symptoms subside earlier.

4. *Tetracyclines* or *erythromycin* may be used in patients who are sensitive to penicillin and should be given for 10 days in full doses.

CAUTION: Sulfonamide drugs should *not* be used for the *treatment* of

established streptococcal infections. Antibiotic troches and lozenges are also *inadequate* for treatment.

III. Prophylaxis Against Bacterial Endocarditis

A. *For dental or oral surgical procedures.*—Penicillin is the drug of choice for patients with rheumatic or congenital heart disease undergoing dental or oral surgical procedures. Doses sufficient to give high levels of penicillin over a period of several days after the procedure are recommended. This excludes the use of benzathine penicillin. Patients should be instructed to report to their physician or clinic should any fever develop within 3 months after the operation. The physician should decide whether treatment for some time before the procedure is indicated.

SUGGESTED REGIMENS (1 is optional; 2 and 3 should be followed in all cases.)

Intramuscular:

1. 600,000 units of procaine penicillin daily for 2 days before surgery.
2. 600,000 units of procaine penicillin intramuscularly 1 hour before the procedure.
3. 600,000 units each day for 2 days after the surgery.

Intramuscular plus oral:

1. 500,000 units of buffered penicillin G or penicillin V orally 4 times a day for 2 days before the surgery.
2. 500,000 units of buffered penicillin G or penicillin V by mouth, supplemented by 600,000 units of crystalline penicillin intramuscularly 1 hour before the procedure.
3. 500,000 units of buffered penicillin G or penicillin V by mouth 4 times a day for 2 days after the surgery.

Contraindications.—Sensitivity to penicillin. In such cases use *erythromycin*, 250 mg. by mouth, 4 times daily for adults and older children. For smaller children use 20 mg./lb./day. Dosage should not exceed 1 Gm. daily.

B. *For other procedures* (childbirth, catheterization or surgery of the genitourinary tract).

1. In addition to either of foregoing penicillin regimens, give streptomycin in full doses for 5 days, beginning, when possible, 2 days before the procedure.
2. *Instead* of penicillin, a broad-spectrum antibiotic (tetracycline or chloramphenicol) should be given in full dosage for 5 days, beginning, when possible, 2 days before the surgical procedure.

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